PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 03-899-A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/036418	International filing date *(day/month/year)* 01.11.2004	Priority date *(day/month/year)* 30.10.2003
International Patent Classification (IPC) or national classification and IPC C07C235/08, C07C233/18, C07D303/36, C07C271/22, C07C255/26, A61K31/165, A61P25/28		
Applicant ELAN PHARMACEUTICALS, INC. et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.06.2005	19.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Zervas, B Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

10/575824
International application No.
PCT/US2004/036418

IAP20 Rec'd PCT/PTO 12 APR 2006

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-109 as originally filed

   Claims, Numbers

   1-18 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-18 (all in part), 9-11 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 9-11 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 1-18 (all in part) are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-18 (all in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/036418

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13,17,18
	No:	Claims	14-16
Inventive step (IS)	Yes:	Claims	1-13,17,18
	No:	Claims	14-16
Industrial applicability (IA)	Yes:	Claims	1-8,12-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/US2004/036418

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1 - 18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to the general formula (I) in which the residue R_1-Y- represents a 3,5-difluorobenzyl group.
Consequently, a complete written opinion concerning the present application is limited to those parts of the claims for which a complete international search report was established (Rule 43bis.1(b) with reference to Rule 66.1(e) PCT).
It should in particular be understood that any positive statement as to novelty and/or inventive step exclusively relates to said limited subject-matter.

Claims 9 - 11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 03/029169 A (ELAN PHARMACEUTICALS), 10 April 2003
D2: WO 03/006013 A (ELAN PHARMACEUTICALS), 23 January 2003

1. Novelty

1.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 14 - 16 is not new in the sense of Article 33(2) PCT.
The document D1 (see D1, page 82, line 8 - page 83, line 23) discloses already the preparation of intermediates disclosed in claims 14 - 16.

1.2 The compounds disclosed in to claim 1 and claim 13 (intermediates) are not disclosed in the available prior art. The subject-matter of claims 1 - 13, 17 and 18 is considered as being novel with respect to the prior art.

2. Inventive Step

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 14 - 16 does not involve an inventive step in the sense of Article 33(3) PCT.
The subject-matter of claims 14 - 16 is not novel. Consequently, it cannot involve an inventive step either.

2.2 The subject-matter of claims 1 - 13, 17 and 18 does meet the criteria of Article 33(3) PCT.
In view of the documents D1 and D2, which can both be regarded as representing the closest prior art, the problem underlying the present application can be defined as providing further compounds with beta-secretase inhibiting activity, which are useful in the treatment of Alzheimer's disease and related diseases. To solve the problem the Applicant provides the compounds of the present application, which differ at least in two structural features from the most relevant prior art compounds described in the documents D1 and D2. The provision of the compounds according to claim 1 of the present application as further beta-secretase inhibitors is thus not obvious with regard to the prior art.
Consequently, the provision of the compounds of claim 1, their preparation (claim 12) and the intermediates disclosed in claim 13 involve an inventive step.

3. Industrial Applicability

3.1 The subject-matter of claims 1 - 8 and 12 to 13 is industrial applicable.

3.2 For the assessment of the present claims 9 - 11 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.